TUBERCULOSIS WITH HIV CO-INFECTION

Chest, Abdomen and Neuroimaging Manifestations

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Abstract

The epidemiology of Tuberculosis (TB) is seriously impacted by the human immunodeficiency virus (HIV) co-infection and this has become a significant challenge to manage globally. HIV infected patients have an increased susceptibility to opportunistic infections like TB. As a result of the impaired cellular immunity and the immunological response in HIV - infected patients, the 'classic' imaging features of TB usually seen in HIV-uninfected patients, may present differently. The aim of this review article is to highlight the imaging features which may assist in the diagnosis of TB in patients with HIV co-infection.

Chest Involvement

- PTB diagnosis in HIV+ children relies on clinical and radiological findings
- CXR is the imaging modality of choice in developing countries
- Increased risk of complicated PTB in HIV+ children
- **Imaging Manifestations:**
  - Hilar and/or mediastinal lymphadenopathy (hallmark of primary TB in childhood)
  - Miliary infiltrate
  - Airspace consolidation is nonspecific unless with intrathoracic lymphadenopathy
  - Pleural effusion, more common > age 5 years, typically without infiltrate

Introduction

Tuberculosis (TB) being the leading infectious cause of mortality in HIV infected children, remains an important health problem worldwide (1). In sub-Saharan Africa the incidence of TB has reached epidemic proportions due to the coexistence of the retroviral epidemic (2). HIV infection increases the risk of reactivating latent Mycobacterium tuberculosis (MTB) infection and of rapid TB progression soon after infection or reinfection with MTB (3).

We discuss the common imaging manifestations of TB and HIV co-infection in the chest, abdomen, genitourinary and central nervous system.

Chest Involvement

HIV infected children have an increased risk of developing complicated pulmonary TB and the risk of TB disease increases with severe immune suppression (4). A South African study found that in a setting with high HIV and TB prevalence, hospitalization of culture-confirmed PTB cases is frequently precipitated by pneumococcal (bacterial) co-infection (5).

The radiological diagnosis of pulmonary TB is difficult in HIV-infected children owing to non-specific clinical signs and limited use of the tuberculin skin test (4, 6). Due to the difficulty in obtaining microbiological confirmation of pulmonary TB in HIV-infected children, diagnosis often relies on a combination of clinical and radiological findings (7-8). Chest X-rays are the standard imaging modality of choice for the diagnosis of pulmonary TB in children in developing countries like South Africa, due to the high HIV and TB disease burden and limitations in resources like Computer Tomography (CT) of the chest (1, 4, 6, 9).

The "radiologic hallmark" of primary childhood TB is hilar and/or mediastinal lymphadenopathy on chest X-ray [Fig. 1] (8, 10-11). Other important chest X-ray findings associated with pulmonary TB are miliary infiltrate (nodules <1 mm) [Fig. 2], and pulmonary cavitation [Fig. 3] (7). Air space consolidation is a very non-specific finding in primary PTB, but in combination with intrathoracic lymphadenopathy is highly suggestive of pulmonary TB [Fig1]. Pleural effusions are uncommon in infants and young children and are more common in children over 5 years with

Chest

- Immune Reconstitution Inflammatory Syndrome (IRIS)
  - Paradoxical worsening of clinical and radiological findings due to immune system recovery following anti-retroviral therapy
  - Develop weeks to months after anti-retroviral initiation
  - Difficult to distinguish from MDR-TB or other infections

Abdomen

- Abdominal TB is rapidly progressive & more often fatal in HIV+ patients
- Haematogenous dissemination from distant primary focus (usually lung), or lymphatic spread
- May involve GIT, peritoneum, lymph nodes and/or solid viscera
- Disease spectrum in children differs from adults
- High index of suspicion essential
- Challenging diagnosis which can mimic many conditions
- Diagnostic delay leads to mortality and unnecessary surgery
- Genitourinary TB is common (especially kidneys)
- High risk of opportunistic infections and co-existent tumour in HIV+ patients

pulmonary TB. The characteristic finding is pleural effusion without associated parenchymal infiltration. However; between 20% to 40% of children in this age group may present with pleural effusions associated with parenchymal infiltrate or hilar and/or mediastinal lymphadenopathy (12).

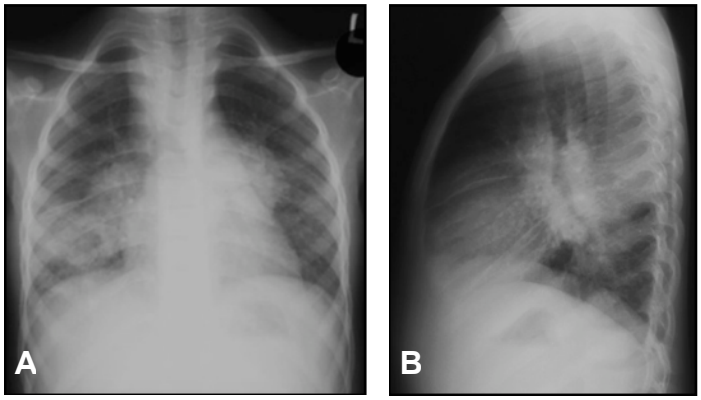

Figure 1. TB lymphadenopathy. Frontal (A) and lateral (B) chest X-ray of child with culture confirmed TB demonstrating hilar and superimposed sub-carinal lymphadenopathy. The frontal chest X-ray (A) demonstrates lobulated, dense masses filling the hilar points. Note the associated right middle lobe consolidation. The lateral view (B) demonstrates the typical “doughnut” sign.

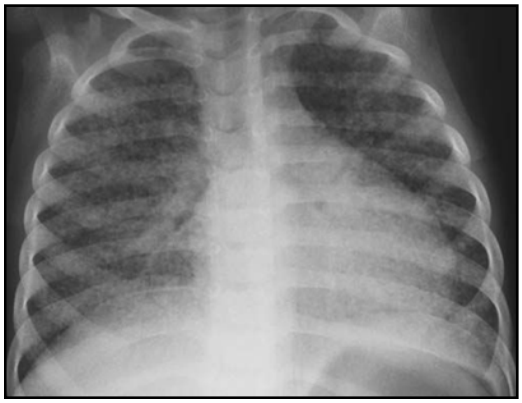

Figure 2. Miliary TB. Chest X-ray in a child demonstrating the classic miliary infiltrates (nodules < 1mm), one of the radiological hallmarks of pulmonary TB.

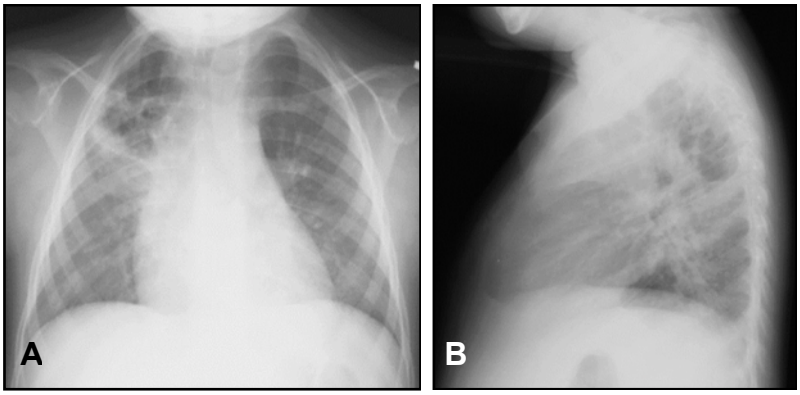

Figure 3. Cavitary Infiltrate. Frontal (A) lateral (B) chest X-ray of child with culture confirmed TB demonstrating multiple upper lobe cavities with associated volume loss.

Abdominal Involvement

- **Imaging Manifestations:**
  - ascites: free or loculated
  - lymphadenopathy with peripheral rim-enhancement is highly suggestive: mesenteric, portal, peri-pancreatic
  - adhesive peritonitis
  - GIT: terminal ileum, caecum
  - Visceral: multi-focal or disseminated disease in liver and/or spleen
    - Organomegaly
    - Micro or larger abscesses
      - CT: diffuse, hypodense focal lesions
      - MRI: T1 hypo, T2 hyperintense, minimally-enhancing
    - Calcified granulomas
  - Differentiation between abdominal TB and lymphoma is difficult and may co-exist in HIV+ patients
  - TB adenopathy often mesenteric with peripheral enhancement and multilocular appearance
  - Lymphoma often para-aortic with homogeneous enhancement
  - TB-IRIS: lymphadenopathy, ascites & psoas abscesses

Immune reconstitution inflammatory syndrome (IRIS) is defined as a paradoxical worsening of clinical symptoms, signs and radiological findings due to the immune system recovery following treatment with antiretroviral therapy, which leads to an abnormal immune response to antigens from dead or dying bacilli. IRIS can occur weeks to months after antiretroviral therapy initiation (4,13). The burden of paradoxical TB-IRIS in children initiating antiretroviral therapy in a sub-Saharan population is low (14). Radiologically, TB-IRIS may present with new hilar or enlarging mediastinal lymph nodes or worsening of pulmonary parenchymal infiltrate, [Fig. 4] or pulmonary nodule enlargement (13). It is important but radiologically difficult to distinguish TB-IRIS from multidrug-resistant TB and other infections like mycobacterial organisms and Cytomegalovirus (CMV) infection (13).

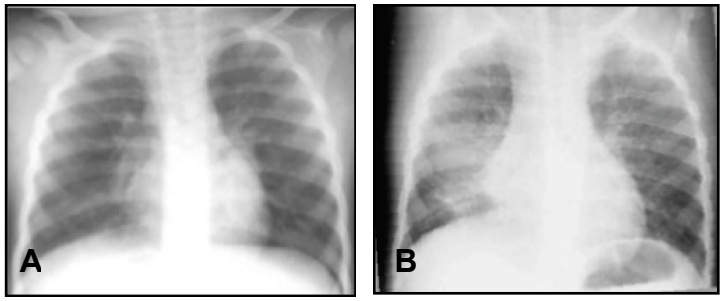

Figure 4. TB-Immune reconstitution inflammatory syndrome (IRIS). Frontal chest X-ray (A) in a 2-year-old child performed as a radiological baseline before the initiation of antiretroviral therapy and frontal chest X-ray (B) performed one month after the initiation of antiretroviral therapy demonstrates significant worsening of hilar lymphadenopathy, associated with right middle lobe consolidation and collapse.

Abdominal Involvement

Abdominal TB is an uncommon manifestation of extra-pulmonary TB. In HIV-infected patients, the disease tends to be rapidly progressive and is more often fatal. Abdominal TB is thought to develop by hematogenous dissemination from a distant primary focus (usually the lung), or via lymphatic spread. It may involve the gastrointestinal tract, peritoneum, lymph nodes and solid viscera, either individually or in combination. The spectrum of disease in children is different from adults, in whom adhesive peritoneal and lymph nodal involvement is more common than gastrointestinal disease (15). The disease can mimic many conditions, making diagnosis challenging. Delay in diagnosis may not only result in mortality but also in unnecessary surgery. A high index of suspicion therefore needs to be maintained (16). Active TB on chest X-ray was found in 4.8% of the cases.

The most common findings on abdominal ultrasound were ascites (87.1%) and mesenteric lymphadenopathy (19.4%) (15). Patients may present with varying imaging features depending upon the organs involved, and CT offers the unique ability to image the entire abdomen in a single examination. Peritoneal involvement may be adhesive or ascitic. The high-density nature

Central Nervous System Involvement

- TB meningitis is the most serious extrapulmonary manifestation
- HIV-infected patients have poor immunological response, and granulomatous reaction is due to the impaired cellular immunity

- **Imaging Manifestations:**
  - Nodular and assymetrical basal meningeal enhancement
  - Tuberculomas are the most common intracranial lesions
  - Tuberculomas affecting meninges are common
  - MRI typically shows low T2 density center and ring enhancement on post contrast
  - More likely to present with cortical infarcts compared to the typical basal ganglia infarcts
  - In addition to communicating hydrocephalus seen in all TB meningitis patients, ventriculomegaly due to HIV encephalopathy can be seen
  - TB-IRIS is a serious complication and should be suspected when there are new or worsening signs with radiological progression in a patient starting antiretroviral therapy

of the fluid is reported by some authors as specific for TB. Ascites can either be free or loculated.

Abdominal lymphadenopathy commonly involves mesenteric, portal and peripancreatic sites reflecting the lymphatic drainage of the small bowel. The nodes may be matted together with hypodense centers, which probably is due to caseation. The pattern of peripheral rim enhancement is highly suggestive of TB (17).

The most common radiological finding of IRIS in patients with TB and HIV co-infection was lymph node enlargement. The intra-abdominal nodes were most commonly involved. These lymph nodes had low attenuation centers (18). Other imaging features that have been encountered are ascites and psoas abscesses.

The most common sites of gastrointestinal tract TB are terminal ileum and cecum, [Fig. 5] (19).

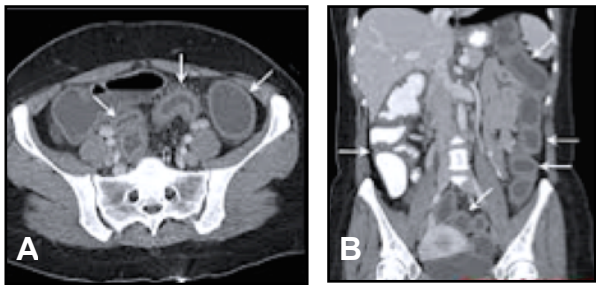

Figure 5. Gastrointestinal TB. Axial (A) and coronal reconstruction (B) CT images demonstrate non-specific findings of bowel wall thickening and enhancement affecting small and large bowel (arrows) in a patient with gastrointestinal TB

Visceral TB is rarely seen in isolation and is more frequently part of multifocal or disseminated disease. Liver and spleen are commonly involved and their involvement can occur in the form of micro abscesses in miliary TB [Fig. 6A], represented on CT as diffuse low density focal lesions [Fig. 6B] or in the form of larger abscesses. Often the only feature of visceral TB is organomegaly with calcified granulomas visible later, or after healing. MRI shows hypo intense and minimally enhancing honeycomb-like lesions on T1-weighted images. On T2-weighted images, the lesions are hyper intense with a less intense rim relative to the surrounding liver.

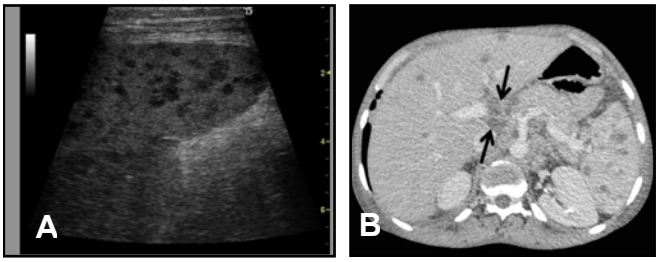

Figure 6. Visceral TB. Ultrasound of the spleen (A) showing multiple micro-abscesses in a patient with abdominal TB. Axial CT scan image of the abdomen (B) demonstrating multiple hypodense lesions in the liver and spleen, as well as periportal lymph nodes with hypodense centers (arrows).

Genitourinary tuberculosis is a common manifestation of extra pulmonary tuberculosis. TB reaches the genitourinary organs, particularly the kidneys haematogenously. The kidneys and possibly the prostate and seminal vesicles are often the primary sites of genitourinary TB. All other genital organs, including the epididymis and bladder, become involved by ascent or descent of infection (20).

Patients with HIV disease have increased incidence of other opportunistic infections (Candida, CMV, atypical Mycobacteria, Cryptosporidium), and coexistent tumor. A variety of aggressive B-cell lymphomas are associated with HIV disease (21). It is not always easy to differentiate TB and lymphoma intra-abdominally. These two conditions may also co-exist in the same patient, in the setting of HIV. Shao et al. demonstrated that abdominal lymphadenopathy tend to be more para-aortic in location in lymphoma and more mesenteric in distribution in TB. Tuberculous lymph nodes also showed peripheral enhancement, and may have a multilocular appearance. In lymphoma, homogeneous, uniform enhancement of lymph nodes is more often seen (22). This enhancement pattern is seen on both CT and MRI (23).

Central Nervous System Involvement

Intracranial TB is due to the hematogenous spread from a primary focus, usually the lungs (24). TB meningitis (TBM) is the most serious extra pulmonary manifestation of TB. CT and MR Imaging plays a significant role in the diagnosis of patients with suspected TB meningitis as well as evaluating complications and in monitoring the progression of the disease (24). The main imaging features of TBM in HIV-uninfected patients are basal meningeal enhancement, infarcts in the basal ganglia and communicating hydrocephalus. Many of the pathological and radiological features of TBM may be explained by the cellular immune and granulomatous response to the tubercle bacilli. The granulomatous response that develops in response to the TB infection is thick and gelatinous and localized predominantly in the basal cisterns and along the middle and anterior cerebral arteries. This typically demonstrates a basal leptomeningeal enhancement pattern often visualized on contrast CT and MRI (25). As HIV infection primarily impairs the cellular immunity, the immunological response to the tuberculous bacilli in these patients may be suboptimal which may result in different clinical and radiological features (26).

The intense basal meningeal enhancement that we often see with the immune -competent children occurs less frequently in the HIV-infected children. HIV-infected children may present with asymmetrical and nodular meningeal enhancement compared to HIV non-infected patients [Fig. 7A] (27-28). Tuberculomas are the most common focal TB lesions seen intracranially. Tuberculomas affecting the meninges are more common in HIV-infected than non-infected patients [Fig. 7B] (27,28). On CT they have a typical iso or hypodense center on CT with ring or discoid enhancement. On MRI the presence of a characteristic T2 hypointense center (due to the paramagnetic effect) with ring enhancement should alert the radiologist to a diagnosis of TB [Fig 8] (29). TB abscesses are rare and have a low-density center on CT and typically demonstrate T2 high signal intensity on MRI. They are difficult to distinguish from other pyogenic abscesses.

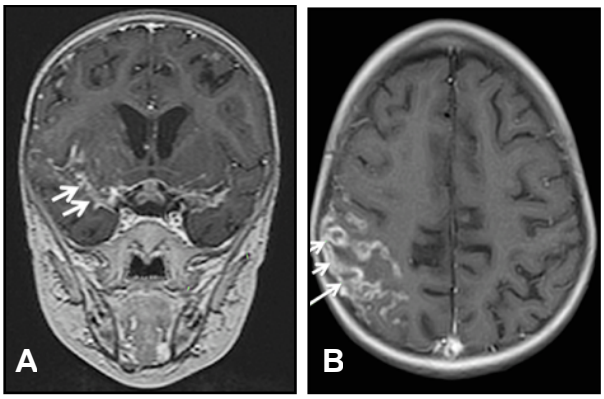

Figure 7. Meningeal Enhancement. Coronal contrast - enhanced T1 MRI (A) shows florid meningeal enhancement most pronounced within the middle cerebral artery cisterns in an asymmetrical pattern, Rt (arrows) more than Lt. Axial Contrast enhanced T1 MRI (B) demonstrates multiple rim enhancing leptomeningeal tuberculomas (arrows).

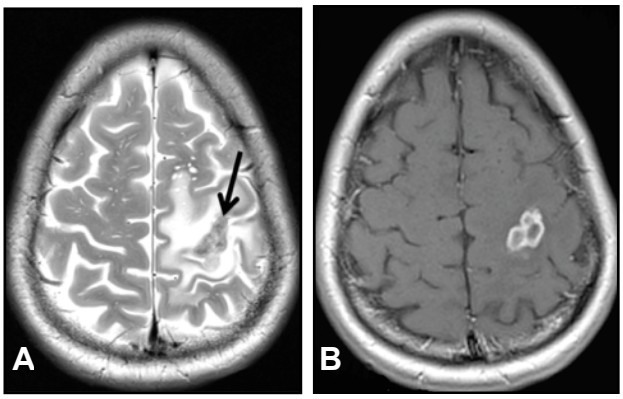

Figure 8. CNS Tuberculoma. Axial T2 weighted MRI (A) demonstrates a tuberculoma with the characteristic central low T2 signal (arrow) and surrounding vasogenic oedema. Axial contrast enhanced MRI (B) shows multi-locular rim enhancement.

Cerebral infarction is a common complication of TBM and the vessels most commonly involved are the perforating vessels at the base of the brain. Garg et al found that HIV-infected patients are more likely to present with cortical cerebral infarcts whilst HIV-uninfected patients predominantly presented with infarcts in the basal ganglia [Fig. 9]. These cortical infarcts in the HIV-infected patients are most likely related to HIV vasculopathy involving medium and large vessels [Fig. 10] (30).

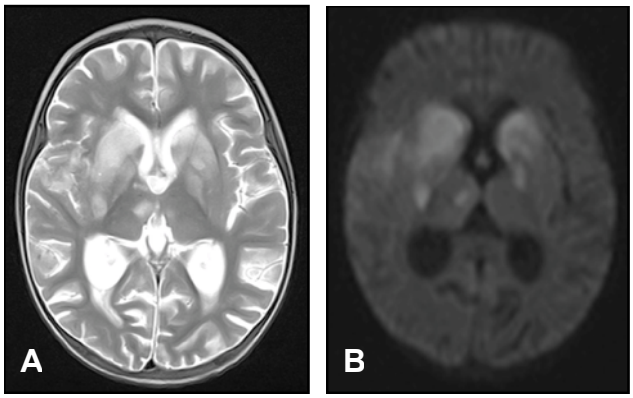

Figure 9. Acute infarcts associated with TB. Axial T2 - weighted MRI (A) and Diffusion-weighted image (B) demonstrates assymmetrical abnormal signal in both basal ganglia and right thalamus indicative of acute ischemic infarcts.

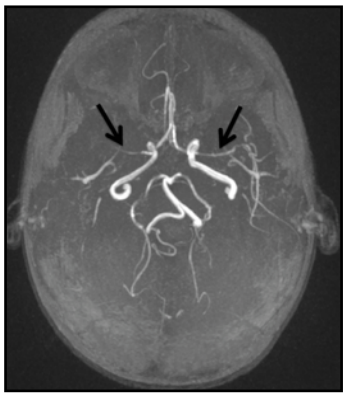

Figure 10. TB CNS Vasculitis. Magnetic resonance angiography using 3D time-of-flight sequence shows narrowing of the proximal left and right middle cerebral artery branches (arrows) compatible with vasculitis.

Hydrocephalus and cerebrospinal fluid obstruction in TBM is caused by the dense and adhesive basal exudate that fills the basal cisterns. Communicating hydrocephalus is seen in more than 80 % of children with TBM. Obstructive hydrocephalus is observed less frequently in HIV-infected children (28, 31). HIV-infected children also develop cerebral atrophy and ventriculomegaly as a result of volume loss. In HIV encephalopathy the degree of atrophy correlates with the viral load and disease severity (28, 31).

Tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) is a common and life-threatening complication in HIV infected children with associated TB of the central nervous system. IRIS symptoms and features often mimic the original infection. TB-IRIS should be suspected when new or worsening neurological signs, new or worsening tuberculous meningitis or new or worsening space-occupying lesion develop shortly after the initiation of antiretroviral therapy (28, 31).

Conclusion

Due to the impaired cellular immunity in HIV infection, there is increased susceptibility to opportunistic infections, TB being the most common. This presents a challenge in diagnosis as the radiological manifestations on imaging for TB infection may present differently, often with multisystem involvement. Imaging, particularly CT and MRI play an important role and should be considered in a child with HIV and atypical presentation of TB.

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